I. Preliminary Remarks

Copies of the foreign priority documents (PCT/IB00/00218 and PCT/IB99/02054) are submitted herewith in accordance with the suggestion of the Examiner.

The specification has been amended to correct an informality identified by the Examiner.

Claim 31 has been amended to incorporate the limitation of dependent claim 32 which has been cancelled and address other informalities in the claim. amended claim 31 is supported at page 13, lines 13-30 of the specification.

Claim 35 has been reformulated as an independent claim and is supported at page 13, lines 31-36 of the specification.

Claim 36 has been reformulated as an independent claim and is directed to a method for the isolation of an intrabody or an intrabody framework wherein the interaction between the two fusion proteins is mediated by a constant region of the library encoded protein. The claim is supported at page 14, lines 1-25 of the specification, page 16, lines 28-35 and in Figure 1 which make it clear that the interaction between the two proteins is antigen independent.

New claims 42-44 are added but do not introduce new matter. Specifically, the subject matter of claim 42 is disclosed at from page 16, line 25 to page 17, line 5, and claims 43 and 44 are supported at page 15, lines 23-28.

II. The Outstanding Rejections

Specifically, the Action makes a formal objection to the specification at page 1 which can be corrected by cancellation of the last two lines of that page.

Claims 31-38 stand as being anticipated under 35 U.S.C. §102(a) by Worn et al., Journal of Biological Chemistry, 275, No. 4 pp 2795-2803 (January 28, 2000)

Claims 31-38 also stand as being anticipated under 35 U.S.C. §102(a) by Taliana et al., Journal of Immunological Methods, 238, pp 161-172 (2000).

Claims 31-38 also stand as being anticipated under 35 U.S.C. §102(e) over Hoffler et al., U.S. Published Application No. 2003/0017149 A1 which is entitled to a reference date as of the filing of its parent which is October 10, 1996.

Claims 31-38 further stand rejected as being anticipated under 35 U.S.C. §102(a) by Visintin et al. PNAS, 96(21):112723-11728 (October 12, 1999) or Cattaneo et al., Trends. Biotech. 17:115-121, (March 1999).

Claims 31-38 are also rejected under 35 U.S.C. §112 (second paragraph) for indefiniteness.

The specification at page 1, last paragraph is objected to as being incomplete.

Finally, the Examiner requested that copies of the foreign priority papers be made of record in order that the application may obtain benefit of its foreign priority filings.

III. Patentability Arguments

A. The Objection to the Specification May be Withdrawn.

The objection to the specification may be withdrawn in light of the amendment to page 1 which deletes text on that page which is duplicative of text at the top of page 2.

B. The Rejections Under 35 U.S.C. §112 (Second Paragraph) Should Be Withdrawn.

The rejections under 35 U.S.C. §112 (second paragraph) for indefiniteness should be withdrawn in light of the amendments to the claims made herein. For example, claim 31 has been rewritten in a manner to delete several of the "wherein" clauses and to recited positive steps of the method. Similarly "marker system" has been deleted from various of the claims and claim 36 has been rewritten in independent form. It is submitted, however, that those of ordinary skill in the art would not find the recitation of "selectable activity" in claim 33 to be

indefinite and similarly that in the context of the invention and in light of the teachings of how to practice that invention in the "transactivation system" and "survival allowing marker" are not indefinite to those of skill in the art.

C. The Rejections of Claims 31-38 Under 35 U.S.C. §102 Should Be Withdrawn.

The present invention is directed to methods for the identification of intrabody frameworks or intrabodies which are soluble and stable and which do not involve any interaction between the antibody and its corresponding antigen. The rejections over each of the cited art references should be withdrawn because all those methods involve an interaction between the antibody and its corresponding epitope of the antigen. In other words, the prior art methods rely upon the interaction of the antibody via its CDR region with the corresponding epitope of the antigen (antigen dependent interaction) as part of its mechanism.

In contrast, the methods of claims 31-35, 43 and 44 are based on the detection of a stable fusion protein comprising a scFv and a marker protein. For example, the method of claim 35 is based on the detection of expression of a marker gene which is under transcriptional control of a scFv-DNA binding fusion protein. This method does not involve any scFv-antigen interaction.

The subject matter of claims 36-38 and 42 differs from the cited prior art in that the interaction between the library encoded protein (comprising the intrabody) and the second fusion protein is mediated via a constant region of the library encoded protein. Specifically, the interaction of the two proteins does not involve the CDR region of the intrabody. (See figure 1) Therefore, the two proteins interact with each other in an antigen independent manner. For these reasons, each of claims 31, 33-38 and 42-44 is novel over the cited art.

The rejection under 35 U.S.C. §102(a) over Worn et al should be withdrawn because that reference shows that anti-GCN4 scFv and mutants thereof can bind the corresponding

antigen in yeast cell i.e., that anti-GCN4 scFv are function in yeast cells. The antigen dependent interaction between the anti-GCN4 scFv and the transcriptional activator GCN4 leads to a reduced transcription of the reporter gene lacZ which is under transcriptional control of the GCN4 protein (p. 2796, left column, second paragraph).

The rejection under 35 U.S.C. §102(a) over Taliana et al should also be withdrawn because that reference discloses a method for the isolation of scFv in yeast cells using the two hybrid system. Such a method is based on an antigen dependent interaction between the scFv and its corresponding antigen (See Taliana Figure 1).

The rejection under 35 U.S.C. §102(a) over Cattaneo should be withdrawn because that reference discloses the intracellular expression of antibodies in mammalian cells. The authors suggest the use of the two hybrid system for the isolation of intracellularly functional antibodies. According to their suggested system, the identification of intrabodies would be based on an antigen dependent interaction between a scFv and its corresponding antigen. (See page 120, left column, fourth paragraph). This is an antigen dependent interaction and does not anticipate Applicants' methods.

The rejection under 35 U.S.C. §102(a) over Visintin et al. should also be withdrawn because it too relies upon the use of the two hybrid system for the isolation of intrabodies wherein the identification of the intrabodies is based on the antigen dependent interaction between the antibody and its corresponding antigen (see *e.g.*, figure 1).

The rejection under 35 U.S.C. §102(a) over U.S. 2003/0017149 should be withdrawn because it too relies upon the use of the two hybrid system for the isolation of intrabodies wherein the identification of the intrabodies is based on the antigen dependent interaction between the antibody and its corresponding antigen.

Not only is the subject matter of the invention novel but the prior art fails to suggest the methods of the invention. The invention provides new methods for the isolation of

soluble and stable intrabodies or intrabody frameworks which surprisingly do not require an interaction between the intrabody and its corresponding antigen. Moreover, claims 35-38 differ from the cited prior art in that the interaction between the second fusion protein and the library encoded protein is mediated via a constant region of the library encoded protein and thus in an antigen independent manner. The antigen independent interaction of the method of claim 35 thus leads to a more efficient method for the isolation of intrabodies or intrabody frameworks compared to the methods described in the prior art since the isolation of intrabodies or intrabody frameworks is only dependent on the stability of the scFv and not on its antigen specificity.

Should the Examiner wish to discuss any issues of form or substance in order to expedite allowance of the pending application, she is invited to contact the undersigned attorney at the number indicated below.

The Commissioner is authorized to charge any fee deficiency required by the paper to Deposit Account No. 13-2855.

Respectfully submitted,

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